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Atypical Antipsychotics for Neuropsychiatric Symptoms of Dementia

Malignant or Maligned?

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Abstract

Recent concerns regarding the use of atypical antipsychotics when used for the treatment of neuropsychiatric symptoms in dementia have led to a flurry of studies attempting to re-evaluate their place in therapy. We critically review current evidence on the safety profiles of these agents in patients with behavioural and psychological symptoms of dementia (BPSD) and provide recommendations to guide the clinician. Potential risks with this class of medications include extrapyramidal symptoms (EPS), weight gain, diabetes mellitus, cardiac conduction abnormalities (e.g. corrected QT [QTc] interval prolongation), cerebrovascular adverse events and mortality. Compared with placebo, treatment of BPSD with atypical antipsychotics leads to little or no increase in EPS and no significant weight change. Compared with typical antipsychotics, treatment of BPSD with atypical antipsychotics leads to a reduced risk of EPS, lower incidences of tardive dyskinesias and no significant weight gain. Atypical antipsychotics have not been associated with glucose intolerance, diabetes or hyperlipidaemia in elderly dementia patients. Both typical and atypical antipsychotics have been associated with cardiac conduction abnormalities, with the magnitude of QTc prolongation being slightly smaller with atypical antipsychotics. Randomised controlled trials suggest that atypical antipsychotics are associated with an increased risk of cerebrovascular adverse events, such as stroke, and an increased mortality compared with placebo. However, it appears that typical antipsychotics have similar risks of cerebrovascular adverse events and death. An increased risk of anticholinergic adverse effects and falls must also be considered with both typical and atypical antipsychotics. In summary, atypical antipsychotics are associated with potentially serious adverse events. Before prescribing these medications in elderly dementia patients, baseline EPS, ECG abnormalities and concomitant medications should be assessed, and the presence of cardiovascular, cerebrovascular and metabolic risk factors should be taken into consideration when benefits and risks are being weighed.

1. Background

The neuropsychiatric symptoms of dementia include agitation, aggression, hallucinations, misidentifications, apathy, depression and anxiety. These disturbances, also known as behavioural and psychological symptoms of dementia (BPSD), are common serious problems that impair the quality of life for patients and their caregivers and lead to premature institutionalisation.[1] Treatment guidelines for BPSD have generally recommended careful assessment and diagnosis, non-pharmacological treatment approaches and psychopharmacological interventions.[2-6] Although a variety of pharmacological approaches exists, the majority of published research has focused on the use of antipsychotics for agitation, aggression and psychotic symptoms. The largest number of published randomised controlled trials (RCTs), published in the 1980s and 1990s, involved typical antipsychotics such as haloperidol and suggested significant but modest benefit compared with placebo.[7] Therefore, it was not surprising that following the introduction of atypical antipsychotics into clinical practice, given their perceived advantages with respect to extrapyramidal symptoms (EPS), RCTs for their use in BPSD would be developed. In fact, although fewer trials with atypical antipsychotics have been published to date, the numbers of patients in these trials dwarf the numbers in the earlier typical antipsychotics trials. There has been a shift in the recommendations in favour of the atypical antipsychotics in large part due to the positive efficacy and apparent safety documented in these trials.[8] Indeed, the use of atypical antipsychotics for BPSD in the elderly appears to have increased dramatically over the past decade.[9]

Unfortunately, evidence of efficacy has been tempered by the emerging data about safety concerns that arose from the pooled data of the BPSD RCTs. Concerns about increased risks of cerebrovascular adverse events in 2002[10,11] were followed by concerns about increased mortality in 2004.[12,13] These concerns understandably preoccupied clinicians, who were already aware of the well known adverse events with atypical antipsychotics, such as weight gain, diabetes mellitus and hyperlipidaemia, which had been highlighted by the schizophrenia RCTs. Therefore, it is not surprising that some health regulatory agencies and authors have argued that atypical antipsychotics should not be used for the treatment of BPSD.[14,15] Others have taken a different approach, suggesting that use of atypical antipsychotics is justifiable after consideration is given to other treatment approaches and after weighing the potential benefits and risks for the individual patient.[15,16]

The purpose of this review is to provide clinicians with more information to help them assess the risks for their individual patients. We have assumed that appropriate assessment and diagnosis have occurred and, where possible, appropriate environmental and behavioural approaches have been utilised. If severe or disturbing agitation, aggression or psychosis persists, pharmacological intervention is warranted and the bulk of evidence exists for treatment with an antipsychotic.[4] Therefore, this review focuses on the safety profiles of atypical antipsychotics, both absolute and relative to the typical antipsychotics. We examine EPS, weight gain, diabetes, corrected QT (QTc) interval prolongation, cerebrovascular adverse events and mortality.

We performed a literature review using the PubMed and EMBASE databases that included articles in English, human research and publications from 1990 to December 2005. Specific search terms included the following: 'dementia' OR 'Alzheimer's disease', 'therapy' OR 'treatment', 'sleep', 'depression', 'anxiety', 'agitation', 'disinhibition', 'aggression', 'delusions', 'hallucinations', 'behaviour', 'antipsychotics', 'neuroleptics', 'risperidone', 'olanzapine', 'quetiapine', 'adverse events', 'extrapyramidal symptoms', 'falls', 'weight gain', 'diabetes mellitus', 'QTc prolongation', 'cerebrovascular adverse events', 'stroke' and 'mortality'. The focus of this review is mostly on risperidone and olanzapine, medications for which published RCT data are available, though quetiapine is included wherever possible. At the time of completion of this review, there were no published trials of ziprasidone or aripiprazole for BPSD.

2. Extrapyramidal Symptoms

Despite the documented efficacy of typical antipsychotics for the treatment of BPSD, it has been well documented that treatment is limited by significant acute EPS, including parkinsonism, akathisia and dystonias, and chronic EPS, such as tardive dyskinesia.[17] Data from RCTs and cohort studies appear to confirm the hypothesised benefits of the atypical antipsychotics with respect to these adverse events. In three large RCTs of risperidone at average dosages of 1 mg/day, there were no increases in EPS compared with placebo.[18-20] One study that included haloperidol as an internal control found that while haloperidol 1mg was as effective as risperidone it caused significantly more EPS.[19] The relative benefit of risperidone over haloperidol for EPS appears to be dose related: a study that included risperidone 2mg demonstrated greater efficacy than risperidone 1mg but more EPS compared with placebo.[18] In two RCTs of olanzapine, there were no increases in EPS compared with placebo at dosages that ranged from 5 to 15 mg/day.[21,22] Similarly, in a third RCT that compared intramuscular olanzapine with intramuscular lorazepam or placebo, there were no significant increases in EPS.[23]

A large retrospective cohort study of 25 000 elderly patients with dementia suggested that although patients treated with typical antipsychotics were 30% more likely to develop parkinsonism than patients treated with atypical antipsychotics, untreated patients were 60% less likely to develop parkinsonism than those treated with either type of antipsychotic.[24] This study also suggested that patients treated with higher doses of atypical antipsychotics (e.g. risperidone ≥2mg) had similar risks of developing parkinsonism as those treated with typical antipsychotics, confirming the dose-response relationship mentioned previously. Perhaps most surprising, the overall event rates (number of events per 100 person-years of follow-up) in this study were low: 4.27 for typical antipsychotics, 3.54 for atypical antipsychotics and 1.27 for untreated patients.

It is well known that increased age, female sex and neurodegenerative disorders all increase the risk of developing tardive dyskinesia following treatment with antipsychotics.[17] Studies suggest that the elderly are at high risk for developing tardive dyskinesia, with cumulative incidence rates of 26% at 1 year and 60% at 3 years.[25] In a prospective longitudinal study comparing the 6-month cumulative incidence rates of tardive dyskinesia in elderly patients with various diagnoses, patients treated with risperidone were significantly less likely to develop tardive dyskinesia than patients treated with haloperidol.[26] Although all of the RCTs for BPSD were short term (3 months), there are some data from the open-label, long-term follow-up studies that were completed after the RCTs.[27,28] These studies suggest that even after up to 1 year of continuous use of atypical antipsychotics, the incidence of tardive dyskinesia is very low. For example, in an open-label follow-up of 255 patients treated with risperidone, the 1-year cumulative incidence rate of tardive dyskinesia was 2.6%, and patients who had tardive dyskinesia at baseline experienced significant reductions in the severity of dyskinesias.[27] Similarly, in the olanzapine follow-up study there were no increases in the severity of baseline dyskinesias after an additional 16 weeks of treatment and, in fact, akathisia decreased significantly over that period of time.[28]

In summary, although acute EPS such as parkinsonism do occur with the use of atypical antipsychotics, these symptoms are less likely to occur during treatment with atypical than typical antipsychotics and the risk can be attenuated by using lower doses. Tardive dyskinesia appears to be infrequent and less common in patients treated with atypical antipsychotics than in patients treated with typical antipsychotics, but more prospective data are required to clarify this risk. Finally, although these observations pertain to most patients with Alzheimer's disease, patients with dementia with Lewy bodies or Parkinson's disease dementia can experience severe 'neuroleptic sensitivity reactions' to low doses of typical and even atypical antipsychotics.[29]

3. Weight Gain

The first characteristic adverse event associated with treatment with atypical antipsychotics noted in the schizophrenia RCTs was significant weight gain. This did not appear to be a class effect, as different atypical antipsychotics have different propensities to cause this adverse drug reaction (ADR). For example, in a meta-analysis of the schizophrenia RCTs, the average weight increases after 10 weeks of therapy for each atypical antipsychotic were clozapine 4.45kg, olanzapine 4.15kg, risperidone 2.1kg and ziprasidone 0.04kg, compared with an average weight loss of 0.74kg with placebo.[30] However, weight gain appears to be less of a concern in elderly populations. For example, in an RCT of 175 elderly schizophrenic patients with a mean age of 71 years, the average weight gain was 0.6kg in risperidone-treated patients and 1.4kg in olanzapine-treated patients.[31] Similarly, in an open-label 12-month study of risperidone in 180 elderly schizophrenic patients with an average age of 72 years, there was no significant weight gain compared with baseline.[32] There are even stronger data to suggest that weight gain is not a problem associated with treatment of BPSD with atypical antipsychotics. For example, in two BPSD RCTs with risperidone[18,19] and two BPSD RCTs with olanzapine,[21,22] there was no significant weight gain compared with placebo. In another BPSD RCT, although patients treated with placebo experienced significant weight loss over 12 weeks, risperidone-treated patients had no change in weight.[20] In a head-to-head study of risperidone and olanzapine, there was no significant difference between placebo (0.1kg loss) and risperidone (0.1kg gain), though olanzapine patients did gain a small but significantly greater amount of weight (1.0kg).[33] Finally, in a retrospective review of institutionalised dementia patients with an average age of 84 years, risperidone-treated patients lost an average of 1.4kg with an overall incidence of weight gain of 0% compared with olanzapine-treated patients, who lost an average of 0.5kg with an overall incidence of weight gain of 0% as well.[34]

In summary, elderly patients with dementia treated with atypical antipsychotics do not appear to experience significant weight gain. It is possible that many of these patients are already significantly below their ideal bodyweight and continue to experience loss of weight as a result of the underlying dementia.

4. Glucose Intolerance/ Diabetes Mellitus

One of the most serious ADRs associated with atypical antipsychotic therapy of schizophrenia is the development of glucose intolerance and diabetes, occasionally even leading to diabetic ketoacidosis and death.[35] This ADR is often, though not always, associated with significant weight gain. Once again, atypical antipsychotics vary with respect to their propensity to cause this ADR. For example, in a large incidence study, the odds ratio for developing diabetes in treated patients compared with untreated patients was 7.44 for clozapine, 3.1 for olanzapine, 0.88 for risperidone and 2.13–3.46 for typical antipsychotics.[36] Similar results were noted in a prevalence study of schizophrenic patients treated for 4 months, though surprisingly, in this study when patients >70 years of age were examined separately, clozapine, olanzapine, quetiapine and risperidone did not significantly increase the risk of diabetes.[37] This pattern was confirmed in a retrospective administrative database study of 10 000 long-term care residents with an average age of 85 years who were treated with typical antipsychotics, atypical antipsychotics or benzodiazepines.[38] Treatment with either typical or atypical antipsychotics did not significantly increase the risk of developing diabetes compared with benzodiazepine treatment. Similarly, in the three risperidone BPSD RCTs,[18-20] the two olanzapine trials[21,22] and the head-to-head study,[33] there was no increase in serum glucose levels noted in drug-treated patients compared with those receiving placebo.

In summary, there is little evidence that the use of atypical antipsychotics is associated with the risk of

glucose intolerance and diabetes noted in younger schizophrenic patient populations.

5. Hyperlipidaemia

Significant increases in serum triglyceride levels have been associated with treatment of schizophrenia with olanzapine and clozapine.[35] These increases are often not associated with increased cholesterol, and the relationship with weight gain is unclear. In a study of lipid abnormalities in elderly schizophrenic patients with an average age of 72 years treated with olanzapine, there were no significant increases noted in either serum triglyceride or cholesterol levels compared with baseline.[39] Similarly, the BPSD RCTs of risperidone[18-20] and olanzapine[21,22] demonstrated no significant changes in serum lipid levels compared with placebo. In fact, in the head-to-head study, treatment with olanzapine and risperidone was associated with significant decreases in total cholesterol levels compared with baseline.[33]

In summary, similar to the other metabolic ADRs of weight gain and diabetes, there appears to be little evidence that elderly dementia patients treated with atypical antipsychotics experience significant hyperlipidaemia.

6. Lengthened Corrected QT (QTc) Interval and Sudden Death

A QTc interval of >500ms (as measured on an ECG) increases the risk of potentially lethal arrhythmias such as torsades des pointes and sudden cardiac death.[40] The propensity for antipsychotics to lengthen the QTc interval has recently received significant scrutiny. In fact, a number of older typical antipsychotics have recently been withdrawn because of this ADR (e.g. thioridazine and pimozide) and some new atypical antipsychotics have failed to be approved (e.g. sertindole). In a large study of QTc changes in younger individuals, the average lengthening of the QTc interval for each antipsychotic was haloperidol 4.7ms, olanzapine 6.8ms, risperidone 11.6ms, quetiapine 14.5ms, ziprasidone 20.3ms and thioridazine 35.6ms.[41] In a study of 20 elderly patients with an average age of 70 years, treatment with risperidone increased the QTc interval by 9ms, with an average post-treatment QTc interval of 426ms. Only one asymptomatic patient experienced a QTc >500ms and, more importantly according to these authors, there was no effect on QT dispersion, a measure correlated with mortality in the elderly.[42] In a troubling study of antipsychotics and risk for sudden cardiac death that included some elderly patients, current use of >100mg equivalents of chlorpromazine more than doubled the risk of sudden cardiac death compared with non-treated patients.[43] A history of cardiac disease increased the incidence of death by 60% in every cohort in that study. Perhaps somewhat reassuring is that there were no recorded changes in ECG parameters reported in the published BPSD RCTs of risperidone[18-20] and olanzapine.[21,22] These results are supported by a large case-controlled study of patients >65 years of age that examined the risk of hospitalisation for ventricular arrhythmias or cardiac arrest.[44] There was no increased risk associated with treatment with atypical antipsychotics compared with no use, while treatment with typical antipsychotics increased the risk by 86% compared with no use and more than doubled the risk compared with treatment with atypical antipsychotics.

In summary, while treatment with atypical antipsychotics has some risk of lengthening the QTc interval, it may not significantly increase the risk of cardiac arrhythmias and appears safer than treatment with typical antipsychotics. Clinicians should consider specific risk factors such as a history of cardiac disease, prolonged QTc interval at baseline and concomitant treatment with medications that prolong QTc themselves or inhibit the metabolism of atypical antipsychotics.

7. Cerebrovascular Adverse Events

Beginning in 2002, after reviewing data from both published and unpublished BPSD RCTs, health regulatory agencies raised concerns about cerebrovascular adverse events associated with risperidone[10] and olanzapine.[11] In 11 RCTs of olanzapine and risperidone (five published, six unpublished), 48 of 2187 (2.2%) drug-treated patients

experienced cerebrovascular adverse events compared with 10 of 1190 (0.8%) placebo-treated patients, suggesting a relative risk of 2.7 (95% CI 1.4, 5.3).[16] These studies have been reviewed in detail elsewhere.[16] The six placebo-controlled trials with risperidone suggested a relative risk of 3.2 when all cerebrovascular adverse events were examined separately. However, when serious cerebrovascular adverse events, defined as death, life threatening, requiring hospitalisation or leading to permanent disability, were examined the relative risk of risperidone treatment was not significantly greater than that with placebo treatment. In the five olanzapine trials, the relative risk of cerebrovascular adverse events was 1.8 (95% CI 0.5, 6.3), which was not statistically significant ($p = 0.36$). Many of these studies, and in particular the risperidone trials, included patients with serious vascular risk factors such as hypertension, diabetes, atrial fibrillation and previous strokes that were untreated or inadequately treated. Although randomisation in these trials should have distributed these patients evenly between placebo and active treatment, it is possible that randomisation was inadequate for some of these features. It is also important to note that the signal for cerebrovascular adverse events was detected *post hoc*, required pooling of data from multiple trials and suffered from multiple comparisons. Furthermore, there is no evidence to date to support any of the proposed mechanisms for this ADR, which would include thromboembolic effects, cardiovascular effects (e.g. orthostatic hypertension, arrhythmias), excess sedation resulting in dehydration and haemoconcentration and hyperprolactinaemia.[16] In spite of these caveats, results from randomised, placebo-controlled trials cannot be dismissed out of hand.

It is interesting to note that several large administrative database studies have not confirmed the association between atypical antipsychotic use and cerebrovascular accidents. For example, in a study comparing 1130 nursing home patients with stroke or transient ischaemic attacks with 3658 control patients, there was no significantly increased risk of cerebrovascular adverse events for patients treated with risperidone, olanzapine, other atypical antipsychotics or typical antipsychotics.[45] Pre-existing cerebrovascular risk factors did appear to increase the risk of cerebrovascular adverse events with antipsychotics other than risperidone. In a large observational cohort study of dementia patients treated with risperidone, quetiapine or olanzapine, there were no differences in the relative risk of cerebrovascular adverse events or transient ischaemic attacks in the first 180 days of treatment among any of these agents.[46] Two other retrospective cohort studies concluded that there was no difference between atypical antipsychotics and typical antipsychotics with respect to the risk of hospitalisation for completed stroke.[47,48] In the larger of these two studies, 17 000 patients who received an atypical antipsychotic were compared with 14 000 patients who received a typical antipsychotic.[48] The adjusted hazard ratio in this study was 1.01 (95% CI 0.81, 1.2), although perhaps most interestingly, in a subgroup analysis of individuals deemed at high risk for stroke (pre-existing stroke risk factors such as hypertension, atrial fibrillation, diabetes and prior stroke), patients treated with atypical antipsychotics were not at an increased risk of stroke compared with users of typical antipsychotics. Although these studies must be interpreted recognising the biases that can arise with these study designs, it is important to note that the risks suggested by the RCTs do not seem to be confirmed.

In summary, results from BPSD RCTs suggest an increased risk of cerebrovascular adverse events with olanzapine and risperidone. While the overall rate is higher with drug treatment, this may not include an increased rate of serious cerebrovascular adverse events such as completed stroke. Observational studies have not confirmed this increased risk and the mechanism of action whereby atypical antipsychotics would lead to cerebrovascular adverse events is unclear. It does not appear that typical antipsychotics provide any relative protection from this potentially serious ADR. Finally, it is still unclear whether pre-existing cerebrovascular risk factors increase the relative risk of cerebrovascular adverse events in patients treated with atypical antipsychotics.

8. Mortality

In May 2004, the US FDA released a warning about the increased risk of mortality with atypical antipsychotics based on 17 placebo-controlled trials of olanzapine, aripiprazole, risperidone and quetiapine in elderly patients with dementia.[12] The mortality rate of 4.5% was almost double the 2.6% rate in placebo-treated patients, with death due to cardiovascular problems such as congestive heart failure, sudden death and infections such as pneumonia. Data released from Health Canada suggested that the increased mortality was noted with risperidone (six trials: risperidone 40/1009 [4%] vs placebo 22/712 [3.1%]), quetiapine (two trials: quetiapine 20/365 [5.5%] vs placebo 7/217 [3.2%]) and olanzapine (five trials: olanzapine 42/1184 [3.5%] vs placebo 7/478 [1.5%]) [aripiprazole studies were not examined as this drug was not approved in Canada at the time of the warnings].[13] A recently published meta-analysis of 15 BPSD RCTs (including nine unpublished studies) of aripiprazole (n = 3), olanzapine (n = 5), quetiapine (n = 3) and risperidone (n = 5) compared 3353 drug-treated patients with 1757 placebo-treated patients.[49] There were 118 (3.5%) deaths with atypical antipsychotics compared with 40 (2.3%) deaths with placebo, suggesting that active treatment was associated with a 54% increase in mortality. There was no evidence that risk varied by drug, severity or diagnosis, and a similar magnitude of risk was noted in two studies that included haloperidol arms. These authors note that the absolute risk difference of 1% implies a number needed to harm of 100 – in other words, there may be one extra death for every 100 patients treated with atypical antipsychotics for 10–12 weeks. The specific causes of death could not be examined in these studies.

Curiously, in contrast to the RCT data, four observational studies found no increase in risk of death associated with atypical antipsychotic treatment.[50-53] In a retrospective 2-year study of 425 elderly patients, the death rates were 47.6% for patients taking typical antipsychotics, 21.9% for those taking atypical antipsychotics and 50% for patients not taking antipsychotics, suggesting that treatment with an atypical antipsychotic actually reduces the mortality risk by 60% compared with non-use.[50]

The relative mortality-sparing effect of atypical antipsychotics compared with typical antipsychotics was also noted in a large retrospective study comparing 299 haloperidol-treated patients with 1254 atypical antipsychotic-treated patients.[51] The 2-year mortality rate in haloperidol-treated patients was 21.4% compared with 4.75% in atypical antipsychotic-treated patients. In a retrospective cohort study of 22 890 patients >65 years of age, risk of death with atypical versus typical antipsychotics was compared at four different timepoints up to 6 months.[53] Typical antipsychotics were associated with a significantly higher adjusted risk of death at all time intervals, with the greatest risk during the first 40 days of treatment.

Finally, in a prospective study of 273 elderly nursing home dementia patients, the 1-year mortality rate in antipsychotic-treated patients was 20.6% compared with 26.8% in non-treated patients.[52] After controlling for a number of variables including age, dementia severity, cognitive impairment, medical comorbidities and BPSD, it appeared that treatment with antipsychotics significantly reduced the risk of 1-year mortality by 23%.

In summary, treatment of BPSD with atypical antipsychotics and possibly typical antipsychotics appears to increase the risk of all-cause mortality based on RCT data. It is unclear from these data whether the risks are modified by underlying patient characteristics (e.g. pre-existing cardiac disease) and the mechanism of action remains elusive. While observational studies published to date fail to confirm this risk, this serious ADR must be considered whenever evaluating the potential benefits and risks of antipsychotic therapy for BPSD.

9. Other Adverse Drug Reactions

A variety of other important potential ADRs associated with atypical antipsychotic treatment of BPSD have been identified. Unlike risperidone, olanzapine has a significant muscarinic M_1 receptor binding capacity *in vitro*, suggesting a potential for

anticholinergic adverse effects *in vivo*.[54] However, anticholinergic-type adverse effects with olanzapine have not been noted in either the study of elderly schizophrenic patients[31] or in the BPSD trials.[21,22]

In a 6-week RCT of olanzapine or risperidone for BPSD, only olanzapine was associated with significant increases in serum anticholinergicity.[55] Although there were no significant differences noted in adverse effects, increased anticholinergic activity was associated with an increase in anticholinergic adverse effects and slower performance on one measure of cognition. The clinical significance of the latter is unclear given that overall cognition did not appear to be affected in any of the BPSD RCTs of olanzapine or risperidone. In contrast, in an RCT comparing rivastigmine with quetiapine or placebo for BPSD, treatment with quetiapine was associated with a significant worsening of cognition compared with placebo.[56] It was unclear from the study whether impaired cognition was due to sedation, anticholinergic effects or other effects. Although the effects of atypical antipsychotics on cognition in dementia require further clarification, there is already reasonable evidence that treatment with typical antipsychotics worsens cognition[19] and hastens cognitive decline.[57]

Falls are potentially serious life-threatening events in elderly patients with dementia. Treatment with most psychotropic medications including antipsychotics, benzodiazepines and antidepressants is associated with an increased risk of falls and hip fractures in the elderly.[58-60] In the risperidone BPSD RCTs,[18-20] there was no increase in falls compared with placebo. In fact, in a *post hoc* analysis of one of the trials, there were statistically fewer falls in patients treated with risperidone 1mg (12.7%) than in patients treated with placebo (22.3%).[61] In one of the BPSD RCTs with olanzapine, the risk of abnormal gait was significantly higher with olanzapine treatment and there were more accidental injuries, including falls, with the 15 mg/day dosage.[21] Similarly, in a recent prospective cohort study of 2000 elderly long-term residents, after adjusting for fall risk factors, treatment with risperidone and typical antipsychotics did not significantly increase the risk of falls, while treatment with olanzapine significantly increased the risk of falls by 74%.[62]

Finally, while the risk of venous thromboembolism in young patients using typical antipsychotics is well recognised,[63] there are fewer data in the elderly. In a retrospective cohort study of nursing home residents, risperidone, olanzapine, quetiapine and clozapine all significantly increased the risk of hospitalisations for venous thrombosis and pulmonary embolism, while there was no increased risk in patients treated with phenothiazines or other typical antipsychotics.[44] However, these authors note that the absolute event rates were very low and negative findings with the typical antipsychotics may have been due to doses that were substantially lower than previous reports. In contrast, another population-based study found no increased risk of venous thromboembolism in elderly patients treated with typical or atypical antipsychotics except for haloperidol.[64]

10. Conclusions

This review has focused on a variety of potentially serious ADRs associated with the use of atypical antipsychotics for the treatment of BPSD. While both typical and atypical antipsychotics represent a heterogeneous group of compounds that vary with respect to their pharmacology and clinical characteristics, certain generalities can be drawn. Atypical antipsychotics appear to cause few acute EPS or tardive dyskinesia when used at dosages effective for BPSD (e.g. risperidone ≤1 mg/day, olanzapine ≤10 mg/day). Metabolic ADRs such as weight gain, glucose intolerance, diabetes and hyperlipidaemia do not appear to be a concern in elderly patients with dementia. Cerebrovascular adverse events may be more common although the risk of completed stroke does not appear to be higher with atypical antipsychotics. All-cause mortality is slightly but significantly more common with atypical antipsychotics than placebo. Effects such as anticholinergic symptoms, cognitive impairment and falls may be more common with some atypical antipsychotics than others. Furthermore, this review suggests that there

is no rationale to revert to the use of typical antipsychotics for BPSD given that their use is clearly associated with increased EPS, probably similar rates of cerebrovascular adverse events and mortality, and worsened cognition.

Treatment of BPSD with atypical antipsychotics must not be taken lightly, though we strongly take exception to the opinion that they are nothing more than "a chemical cosh"[15] or the recommendations to avoid their use completely.[14] Psychiatry has an important tradition of recognising factors associated with toxicity and implementing appropriate monitoring. If it were not for this, the use of both lithium and clozapine, two of the most efficacious drugs in psychiatry therapeutics, would have been abandoned. It is only with careful RCTs as well as adequate postmarketing surveillance that accurate data on the incidence of and risk factors for potentially serious adverse effects of these drugs can be elucidated. This is what is currently occurring with atypical antipsychotics for BPSD and helping to inform clinical practice.

How can clinicians incorporate these data into their practice? As noted previously, treatment of BPSD begins with appropriate assessment and diagnosis and use of environmental and behavioural approaches whenever appropriate and practical/possible. If pharmacotherapy is still necessary and target symptoms of agitation, aggression or psychosis are present, treatment with an atypical antipsychotic (at present risperidone or olanzapine) should be considered in preference to a typical antipsychotic. Individual characteristics and risk factors such as baseline cognition and EPS, cardiovascular, cerebrovascular and metabolic risk factors, ECG abnormalities, and concomitant medication should be noted. Substitute decision makers should be informed of the potential benefits and risks. Since, as this review has highlighted, the atypical antipsychotics vary in their propensity to cause certain adverse events, the choice of a specific atypical antipsychotic should be based on the individual vulnerabilities of the patient. Therapy should be initiated at low doses and titrated to the lowest effective dose. Therapy should be re-evaluated every 3 months. In cases where the effectiveness is questionable, the drug should definitely be discontinued. In cases where the effectiveness is clear, consideration should still be given to tapering the dose and/or discontinuing after 3–6 months as there are excellent data from several placebo-controlled RCTs suggesting that treatment can be discontinued in most patients without behavioural exacerbations after a period of behavioural stability.[65-67]

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